

# Ebola cases and health system demand in Liberia

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## Abstract

In 2014, a major epidemic of human Ebola virus disease emerged in West Africa, where human-to-human transmission has now been sustained for greater than 10 months. In the summer of 2014, there was great uncertainty about the answers to several key policy questions concerning the path to containment. What is the relative importance of nosocomial transmission compared with community-acquired infection? How much must hospital capacity increase to provide care for the anticipated patient burden? To which interventions will Ebola transmission be most responsive? What must be done to achieve containment? In recent years, epidemic models have been used to guide public health interventions. But, model-based policy relies on high quality causal understanding of transmission, including the availability of appropriate dynamic transmission models and reliable reporting about the sequence of case incidence for model fitting, which were lacking for this epidemic. To investigate the range of potential transmission scenarios, we developed a multi-type branching process model that incorporates key heterogeneities and time-varying parameters to reflect changing human behavior and deliberate interventions. Ensembles of this model were evaluated at a set of parameters that were both epidemiologically plausible and capable of reproducing the observed trajectory. Results of this model suggest that epidemic outcome depends on both hospital capacity and individual behavior. The model predicts that if hospital capacity is not increased soon, then transmission may outpace the rate of isolation and the ability to provide care for the ill, infectious, and dying. Similarly, containment will probably require individuals to adopt behaviors that increase the rates of case identification and isolation and secure burial of the deceased. Given current knowledge, it is uncertain that this epidemic will be contained even with 99% hospitalization rate at the currently projected hospital capacity.

## Introduction

The 2014 epidemic of Ebola virus in West Africa is an emerging public health and humanitarian crisis of epic dimensions (WHO Ebola Response Team 2014). This epidemic originated in an outbreak in Guéckédou, Guinea in December 2013. The Ministry of Health of Guinea and Médecins Sans Frontières (MSF) were alerted to clusters of an unknown disease with fever/vomiting/diarrhea and a high fatality rate on March 10 and 12, 2014 (Baize et al. 2014). Through human-to-human transmission, the virus subsequently spread to Liberia (29 March; World Health Organization (2014e)), Sierra Leone (25 May; World Health Organization (2014f)), Nigeria (22 July; World Health Organization (2014g)), Senegal (29 August; World Health Organization (2014h)), and the United States (30 September; World Health Organization (2014j)). On 8 August 2014 the World Health Organization declared the epidemic to be “a Public Health Emergency of International Concern” entailing an obligation on the part of 194 signatories to participate in disease prevention, surveillance, control, response and reporting (World Health Organization 2014i). On 6 October, the first transmission outside of Africa was documented in Spain (Gulland 2014). As of 27 October, 13,703 persons are reported (but not confirmed) to have been infected (World Health Organization 2014a) with a fatality rate for those cases with known clinical outcome around 70% (WHO Ebola Response Team 2014). Due to widespread under-reporting, the true number of cases is widely believed to be considerably higher.

Ongoing international support has included the shipment of large quantities of personal protective equipment, diagnostic laboratory apparatus, and materiel such as vehicles; provision of medical and logistical advisors from MSF, the US Centers for Disease Control & Prevention, and the World Health Organization, among others; and the construction of new treatment facilities (UN-OCHA 2014). A range of further clinical interventions, health policies, and aid are under consideration and at various stages of mobilization. Whether these are sufficient to achieve containment and/or what further actions might extend their reach remain unknown. Epidemic modeling provides a means for structured reasoning about such complex dynamical

conditions, both with respect to the information contained in this epidemic’s history to date and prospective opportunities for intervention. While several models of the 2014 West Africa Ebola epidemic have been published, the majority of these are primarily aimed at estimating the basic reproduction number ( $R_0$ ), a summary statistic that may be tremendously informative about the potential rate of spread and the magnitude of vaccination required to achieve herd immunity (Fisman, Khoo, and Tuite 2014). Knowing  $R_0$  is less useful where human behaviors – including both public health interventions (Farrar and Piot 2014) and avoidance or denial in the community (Briand et al. 2014) – cause the epidemic to take a more irregular path. Two models that incorporate more detail have been published. A paper by the WHO Ebola Response Team (2014) proposes a renewal equation for the evolution of the epidemic through time, parameterized with case reports collected by MSF. But this model, which focuses on the time course of disease and conditions for transmission, does not account for role of transmission setting. The model of Meltzer et al. (2014) is more tactical, but provides little analytical insight.

Here, we report on a model of intermediate complexity. Our goal was to produce a model that could be used to guide policy recommendations. A supporting objective was to perform analysis of a range of scenarios to identify how actions taken in the present may influence short and medium term prospects for containment. The model comprises separate probability distributions for the number of secondary cases arising among health care workers (HCW) infected in hospitals, non-HCW infected by hospitalized patients, non-HCW infected during non-hospital nursing care, and non-HCW infected through burial practices. Infected individuals may be treated in the hospital or in the home. Hospital treatment is assumed to result in reduced transmission but is limited to a fixed number of available hospital beds. Cases in excess of hospital capacity are assumed to be treated in the home. Only cases seeking hospitalization (whether capacity allows admission or not) are scored as a report, separating the total number of cases (which is unknown) from the number of cases reported. In contrast to the models of WHO Ebola Response Team (2014) and Meltzer et al. (2014), this model allows for changing human behavior and epidemic interventions through time-varying rates of hospitalization, exposure of health care workers, and secure burial. We use the theory of branching processes to derive an expression for the mean number of secondary infections.

Here we report on the application of this model to the current situation in Liberia. We focus on Liberia for a combination of practical and intellectual reasons. Practically, the international variation in both transmission and response precluded treating the three countries of Liberia, Sierra Leone, and Guinea simultaneously. Additionally, although the situation is uniformly urgent across the three countries, the speed of spread in Liberia during late summer and early fall of 2014 suggest it is the country of greatest need, both with respect to the number of persons at immediate risk of infection and as a probable regional “driver” of large-scale dynamics. Intellectually, we found our modeling work to be facilitated by the consistent collection of data in Liberia since late June with timely and disaggregated reporting, high level coverage in the American news media, and clear plan for the expansion of hospital capacity.

## Methods

### Data

Data were obtained from situation reports issued by the World Health Organisation and the Liberia Ministry of Health. All situation reports were pulled from Liberian MoH website or United Nations Office for the Coordination of Humanitarian Affairs (UN-OCHA) provided websites (reliefweb.int and humanitarianresponse.info). When values had to be interpolated, data from WHO outbreak reports were used. For provenance and reproducibility, we digitally entered our own data, which are available from the Dryad Digital Repository at [URL/DOI TO BE PROVIDED]. Reported cases were scored as the sum of suspected, probable, and confirmed cases.

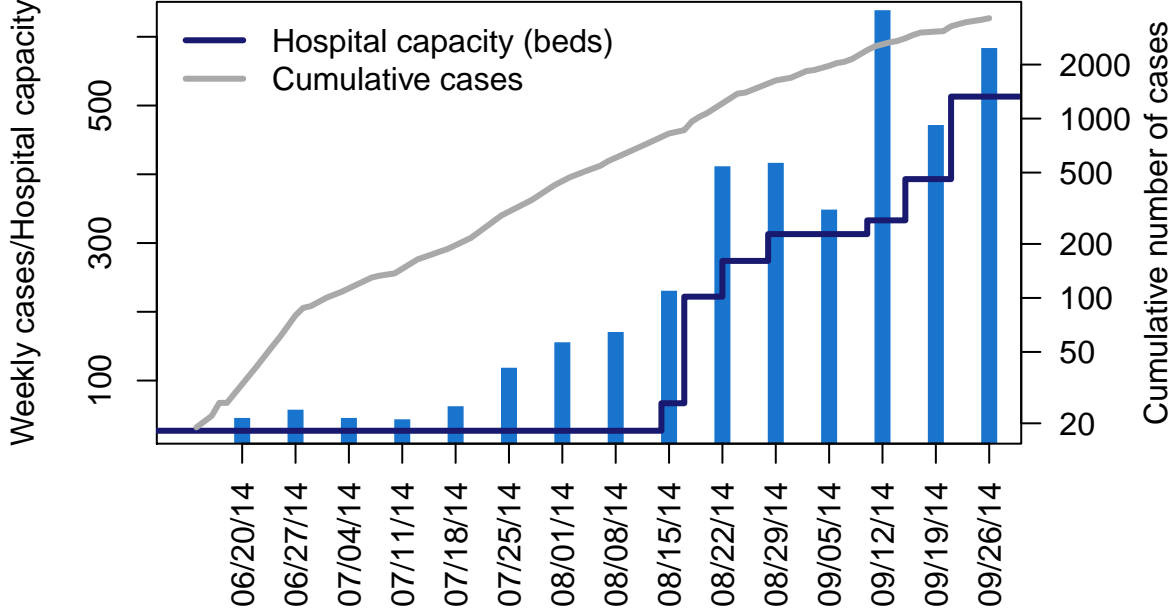


Figure 1: Weekly number of suspected, probable, and confirmed cases of Ebola virus in Liberia in the seven days terminating with each date (blue bars) and daily cumulative reports (gray line); data from WHO situation reports. Hospital capacity in Ebola treatment units (total number of beds in country, dark blue line); data compiled from media and government sources.

## A branching process model

### Model

We developed a discrete time, stochastic process model for Ebola transmission. The model considers where transmission occurs and who is infected as a result. This allows a minimal set of subpopulation differences to be articulated that nonetheless reflect the major epidemiological properties of Ebola transmission, including hospital treatment versus community care, transmission at funerals, and scenario-dependent transmission risk differences during care-giving. The model comprises separate probability distributions for the number of secondary cases arising from (1) health care workers (HCW) infected in hospitals, (2) non-HCW infected by hospitalized patients, (3) non-HCW infected during non-hospital nursing care, (4) non-HCW infected through burial practices. Infected individuals are considered to be treated either in the hospital or in the home (Figure 2).

Specifically, our model supposes that transmission is comprised of five processes that result in 11 state transitions (Figure 2). In the following description, numbers in parentheses correspond to labels in Figure 2.

- Persons treated in the community give rise to a Poisson distributed number of secondary infections among community members at rate  $\lambda = Nq$ , where  $N$  is the number of contacts and  $q$  is the per contact probability of transmission. To accommodate heterogeneity in transmission,  $\lambda$  may be taken to be a random variable, in which case the number of secondary infections is negative binomially distributed with an additional parameter,  $\theta$ , regulating dispersion (1).
- Persons treated in the hospital give rise to a Poisson distributed number of secondary infections among health care workers at rate  $\lambda\beta\alpha$ , where  $\beta$  is a multiplier for the additional contacts acquired through hospitalization and  $\alpha$  is a multiplier for the effect of infection control interventions (2).
- Persons treated in the hospital may pass infection to a Poisson distributed number of visitors at rate  $\lambda_h$  (3). It is assumed that all deceased hospitalized patients are given a secure burial.
- Persons treated in the community recover or are given a secure burial at rate  $g$  (and therefore do not

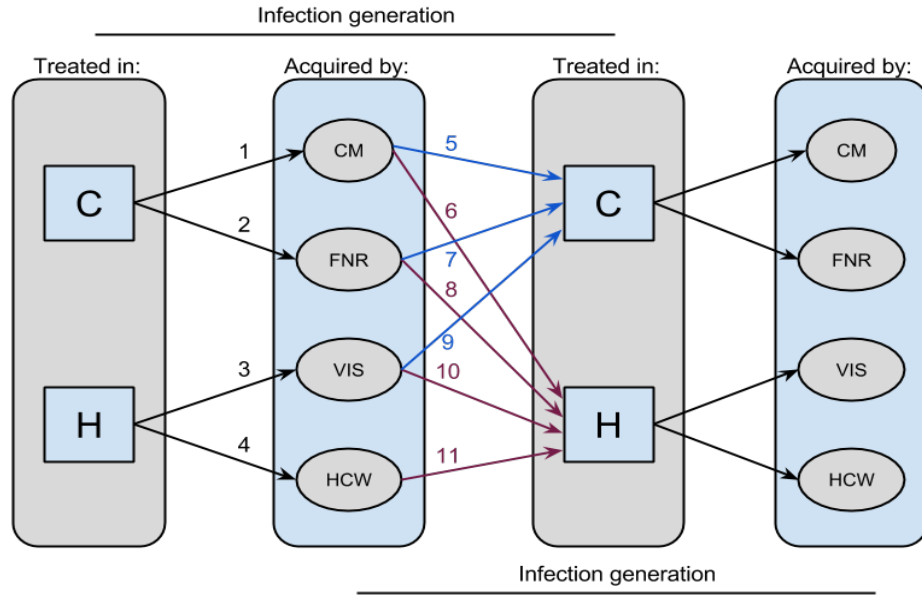


Figure 2: Structure of a model for human-to-human transmission of Ebola virus. Flow of transmission is depicted through two generations of infection in a multi-type branching process model of Ebola virus transmission. Grey panels show that infected persons may be treated in either the community (C, blue paths) or hospital (H, purple paths). Community treated patients may give rise to secondary infections in community members through nursing care (CM) or in the process of body preparation and burial (FNR). Hospital-treated patients may give rise to secondary infections in health care workers (HCW) or visitors (VIS). Infected persons may either be treated in the community or in the hospital at rates that depend on the conditions under which the infection was acquired.

give rise to any further secondary infections) and non-secure burial at rate  $1 - g$ , giving rise to a Poisson distributed number of secondary infections at rate  $\phi$  (4).

- Persons acquiring infection in the community (classes CM, VIS, and FNR) are hospitalized with probability  $h$  (6, 9, 11) or remain in the community with probability  $1 - h$  (5, 8, 10).
- Infected health care workers are all assumed to be hospitalized (7).

These processes constitute a multi-type branching process. Branching process models allow for very flexible specification of the distribution of secondary cases. Branching processes do not account for the depletion of susceptibles at the population level, however, and thus are appropriate during the exponential phase of epidemic spread and/or where spread is controlled through human intervention rather than self-limitation. We believe these assumptions are broadly consistent with the currently prevailing conditions in West Africa.

### Hospital capacity

In simulations, hospital treatment was assumed to result in reduced transmission, limited by the number of available hospital beds. Patients seeking hospitalization in excess of hospital capacity were assumed to be returned to the home for treatment. Only patients seeking hospitalization (whether capacity allowed admission or not) were scored as a report, separating the total number of cases (which in reality is unknown) from the number of cases reported.

### Parameterization

To parameterize this model, we were initially guided by reports on the outbreaks of Ebola virus in Kikwit (Democratic Republic of Congo) in 1995 (Bwaka et al. 1999) and Gulu (Uganda) in 2000-2001 (Oyok 2001).

### Transmission ( $N$ , $q$ , $\theta$ ) and the effectiveness of infection control ( $\alpha$ )

The attack rate in Kikwit was 9% among hospital workers (Tomori et al. 1999) and 16% among family members (Dowell et al. 1999). The ratio of exposures to index cases in households was  $\hat{N} = 173/27 = 6.4$  for 27 different families. Assuming exposure was only within the family (so each secondary case had only one exposure), we have  $\hat{q} = 0.16$  (risk of transmission per contact). At Kikwit General Hospital, 37 of 429 workers met the case definition for Ebola virus disease. A reported three cases occurred after the use of barrier nursing. If we assume that these 3 were all in Kikwit General Hospital, then 34 health care workers were infected prior to infection control. 110 out of 138 other hospital workers reported direct contact with an Ebola patient. Extrapolating to the 392 health care workers who weren't infected, we estimate the number of workers with direct contact to be  $110/138 \times 392 + 34 \approx 346$  yielding an attack rate of 9.8%. Of course, hospital workers experience greater exposure than persons providing care in the community. Among 48 uninfected persons with direct contact jobs at Kikwit General Hospital there were a total of 151 patient contacts (3.15 contacts per worker). If this were representative, then we would have the relation  $1 - (1 - q\alpha)^{3.15} = 0.098$ , yielding  $\alpha = 0.20$  prior to the implementation of barrier nursing and other infection control measures. Following barrier nursing, 3 out of  $110/138 \times 392 + 3 \approx 315$  health care workers were infected, yielding an attack rate of 0.95%. Using the relation  $1 - (1 - q\alpha)^{3.15} = 0.0095$  we obtain  $\alpha = 0.019$  after the implementation of barrier nursing and other infection control measures.

### Hospital contact multiplier ( $\beta$ )

The parameter  $\beta$  relates the number of contacts in a health facility to those in a household and is expressed as a multiplier of  $N$ . This value is chosen based on intuition and narrative reports. In general, we consider values in the range  $2 < \beta < 5$  to be reasonable.

## Funeral transmission ( $\phi$ )

Legrand et al. (2007) assumed that mean duration of death to burial was 2 days and estimated transmission rates of 7.66 per week (Kikwit) and 0.46 per week (Gulu). Translating into average number of infections, the number of secondary cases through funeral are estimated to be 2.18 and 0.13, respectively, assuming  $S/N \approx 1$ , where  $S$  is the number of susceptible individuals in the population and  $N$  is the total population size. A value of  $0 < \phi < 3$  is consistent with the routine finding that preparation of the body constitutes a substantial risk factor and that this duty is performed by a relatively small number of people. We note that this is not consistent with anecdotal reports of large numbers of persons being infected at a funeral. We consider those events most likely to be exceptional. Parameter values of this “core model” are reported in Table 1.

Variable	Value
Household contacts ( $N$ )	6.4
Transmission probability ( $q$ )	0.16
Overdispersion ( $\theta$ )	1
Hospital contact multiplier ( $\beta$ )	4
Effectiveness of infection control ( $\alpha$ )	0.019
Average number of secondary community cases from hospitalized patients ( $\lambda_h$ )	0.3
Average number of secondary cases from a funeral ( $\phi$ )	2.18

Table 1. Parameter values of the basic branching process model for Ebola transmission.

## Treatment facilities

From a range of reports, we compiled a time series of the operational Ebola Treatment Units (ETUs) along with estimates of their capacity, recorded as the number of patient beds available (Figure 1). Importantly, many ETUs were regularly reported to be operating above capacity, typically by around a factor of two (World Health Organization 2014b, Medecins Sans Frontieres (2014), World Health Organization (2014c)). Additionally, the average hospital stay is around 6.5 days (WHO Ebola Response Team 2014), considerably shorter than the 15 day infection generation. Therefore, throughout our analysis, we estimate the number of patients potentially served by an ETU within an infection interval using the formula

$$s(t) = 2b(t)\tau/\sigma \quad (1)$$

where  $t$  marks time in infection generations,  $b(t)$  is hospital capacity in terms of the number of beds,  $\tau = 15$  is infection generation time, and  $\sigma = 6.5$  is the average duration of hospitalization.

## Secure burial rate

Non-secure burial (including body preparation and funeral ceremonies) is one of the key occasions for Ebola virus transmission. The Liberia Ministry of Health and international partners have therefore sought to reduce this mode of transmission through public education about the risk of exposure from deceased Ebola patients and the mobilization of body retrieval and burial teams. It is likely, therefore, that there has already been a reduction in transmission due to increased frequency of secure burial. For example, even during the interval from 4 July to 2 September (prior to a potentially spurious downturn (World Health Organization 2014a)), the cumulative reported number of cases shows a negative curvature on a logarithmic scale (grey line in

Figure 1). We therefore modeled  $g$  (a rate that is the sum of the recovery rate and secure burial rate) using the time-dependent function

$$g(t) = \gamma_1(1 - 1/((t - 7)\gamma_2)) + \mu \quad (2)$$

where  $t$  is measured in terms of infection generations and  $\mu = 0.3$  is one minus the case fatality rate,  $\gamma_1 < 0.7$  is the maximal secure burial rate, and  $\gamma_2$  governs the speed at which safe burials increase. This function allows for the secure burial rate to increase beginning around 4 July, starts at a positive minimum due to natural recovery, and asymptotically approaches a maximum at  $\gamma_1 + \mu$ , since we suppose that secure burial and recovery cannot go to 100%.

### Initial conditions

According to our data, there were 27 beds in ETUs in Liberia on 4 July. Based on the reported cumulative case count, there were approximately  $108 - 30 = 78$  active reported cases at this time. Using equation (1), we estimated that 54 of the reported cases were under hospital care. Further assuming under-reporting by a factor of 2.5 (Meltzer et al. 2014, Chan (2014)), we estimated that there were a total of 195 cases for  $195 - 78 = 117$  unreported cases at this time. Together, these calculations imply that 54 persons were treated in hospitals and 141 persons were treated in the community.

### Other parameters

In general, we treat the hospitalization rate ( $h$ ), secure burial rate ( $\gamma_1$  and  $\gamma_2$ ), funeral transmission  $\phi$ , and overdispersion ( $\theta$ ) as tuning parameters. The time scale of this model is defined with respect to infection generations. To calibrate to calendar time, we assumed a serial interval of 15 days (WHO Ebola Response Team 2014). To calculate hospital capacity, we assumed an average hospital stay of 6.5 days (WHO Ebola Response Team 2014).

### Plausible parameter sets

Guided by these crude parameter estimates, we then tuned our model to data from the 2014 Ebola outbreak in Liberia. There were two waves of transmission in 2014 in Liberia. The first wave occurred in March and April, comprised a total of 8 reported cases, and may have gone extinct in mid-May. The second wave began in late May and was the origin of the vast majority of cases. However, reported cases between the end of the first wave and around 4 July were irregular, whereas after 4 July there was a dramatic and sustained increase in the number of cases for many weeks. Around 6 September, the smoothed average number of cases per case (a model-independent estimate of  $R_{eff}$ ) began to decline (not shown). The World Health Organization Situation Report of 8 October indicates that this decline was probably due to a deterioration in reporting, rather than a true decline in transmission. For these reasons, we focused our fitting on the interval from 4 July 2014 to 2 September 2014. In keeping with the time scale of our model, and to smooth over daily variations in reporting, reported cases were aggregated to 15 day transmission generations (Table 2).

Date	Cumulative cases	Cumulative cases among health care workers
7/4/2014	122	12
7/19/2014	197	20
8/3/2014	498	64
8/18/2014	972	115
9/2/2014	1847	153

Table 2. Reported cases and reported cases among health care workers during five infection generations of the 2014 outbreak of Ebola in West Africa.

The parameters  $h$ ,  $\gamma_1$ ,  $\gamma_2$ ,  $\theta$ ,  $\alpha$  and  $\phi$  were first tuned so that the median simulated reports of infection among health care workers in the four infection generations between 4 July and 2 September and the median simulated number of cumulative reports among non-healthcare workers at the same times were as close to the reported values as possible (see Online Supplement). We further refined these fits by minimizing squared differences on a logarithmic scale. We then used latin hypercube sampling to explore a parameter space within  $\pm 25\%$  of the tuned values. A parameter set was deemed plausible if the reported cumulative number of cases and reported cumulative cases among health care workers were within the observed range of 500 simulations.

## Forecasting

To forecast future cases under different scenarios for aid and intervention, we project cases and number of persons seeking hospitalization from 3 September 2014 until 31 December 2014 (120 days) under five scenarios:

1. *Baseline*. Transmission and hospitalization continue at current levels (hospital capacity of 601 beds);
2. *Scenario A*. Conditions improve due to the U.S. aid commitment of 15 September 2014 (hospital capacity increases by 1,700 beds in Ebola treatment centers between 25 October 2014 and 28 December 2014 to a total of 2,301 beds);
3. *Scenario B*. Conditions improve through an increase in hospital capacity of 6,800 new beds (four times the U.S. aid commitment of 1,700 beds), bringing total hospital capacity to 7,401 bed equivalents by 28 December 2014;
4. *Scenario C*. Conditions improve by increase in hospital capacity to 7,401 bed equivalents by 28 December 2014 and hospital admission rate of 85%.
5. *Scenario D*. Conditions improve by increase in hospital capacity to 7,401 bed equivalents by 28 December 2014 and hospital admission rate of 99%.

Initial conditions for these scenarios were derived from outbreak reports issued by the Liberia Ministry of Health and World Health Organization. Specifically, on 2 September 2014 the number of persons per infection generation that could be treated in ETUs was 1444. In this generation, the number of reported infected persons was  $1871 - 972 = 899$  for a total infection generation of approximately 2248. We assume that, at most, the fraction seeking hospitalization (60.2%) was admitted, yielding  $2248 \times 0.62 \approx 1394$  with  $2248 - 1394 = 854$  remaining in the community.

## Results

### Model fit

Overall, 1,045 of 5,000 (20.9%) parameter sets were determined to be plausible. Mean values from plausible parameter sets are reported in Table 3.

Variable	Value
Hospitalization rate ( $h$ )	0.6
Overdispersion ( $\theta$ )	2.2
Average number of secondary cases from a funeral ( $\phi$ )	5.9
Speed of secure burial improvement ( $\gamma_0$ )	0.6



Variable	Value
Average number of secondary cases from a funeral ( $\phi$ )	6.0
Core secondary transmission rate ( $\lambda$ )	1.1
Hospital leakage ( $\lambda_h$ )	0.25

Table 3. Mean values of plausible parameter sets.

The fit of the tuned model to the cumulative number of reported cases in Liberia is shown in Figure 4. The heavy blue line shows the cumulative number of reported cases. The plausible range of case reports given the model is shown in yellow (95% prediction intervals). The plausible range of total cases, including unreported cases, is shown in blue. The fit of the model to infection generations in health care workers and in the general public is shown in Figure 5.

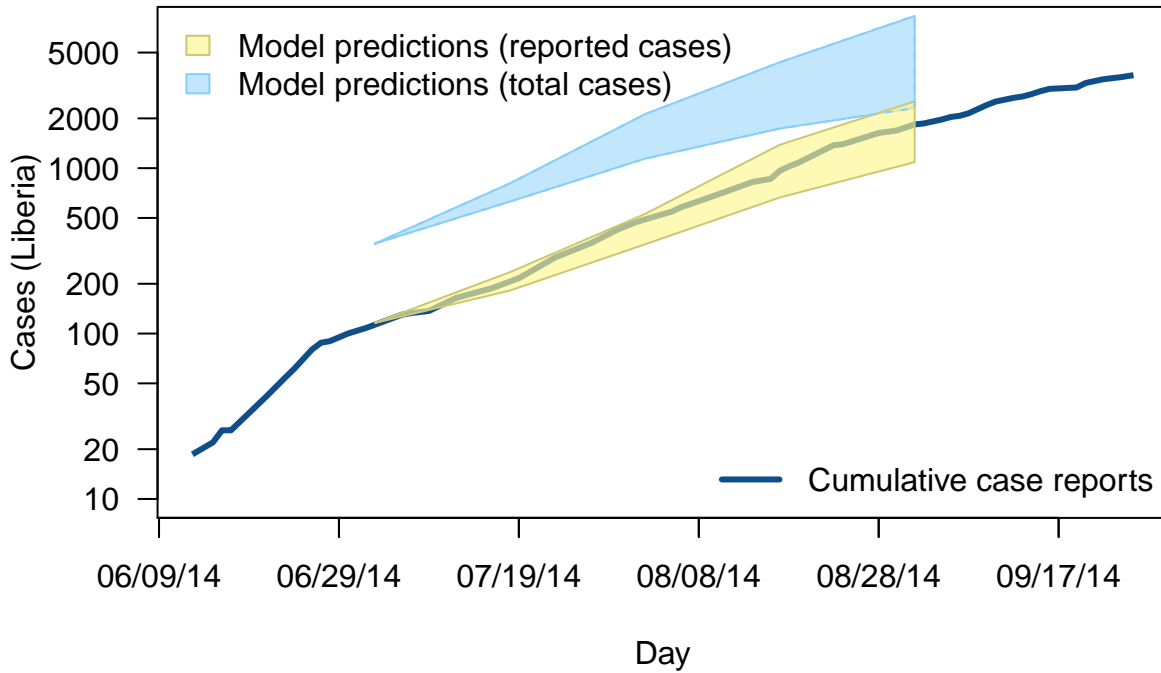


Figure 3: The fit model for Ebola transmission in Liberia initialized on 4 July. The heavy blue line shows the cumulative number of cases reported. The yellow region shows the model-predicted range of cases expected to be reported given incomplete reporting. The blue region shows the model-predicted total number of cases over the same time.

### Effective reproduction number

Model-based effective reproduction numbers at infection generations between 4 July and 17 October were calculated by evaluating the effective reproduction number (see online supplement) at the 1,045 plausible parameter sets. The change over time in the range of plausible effective reproduction numbers is shown in Figure 3.

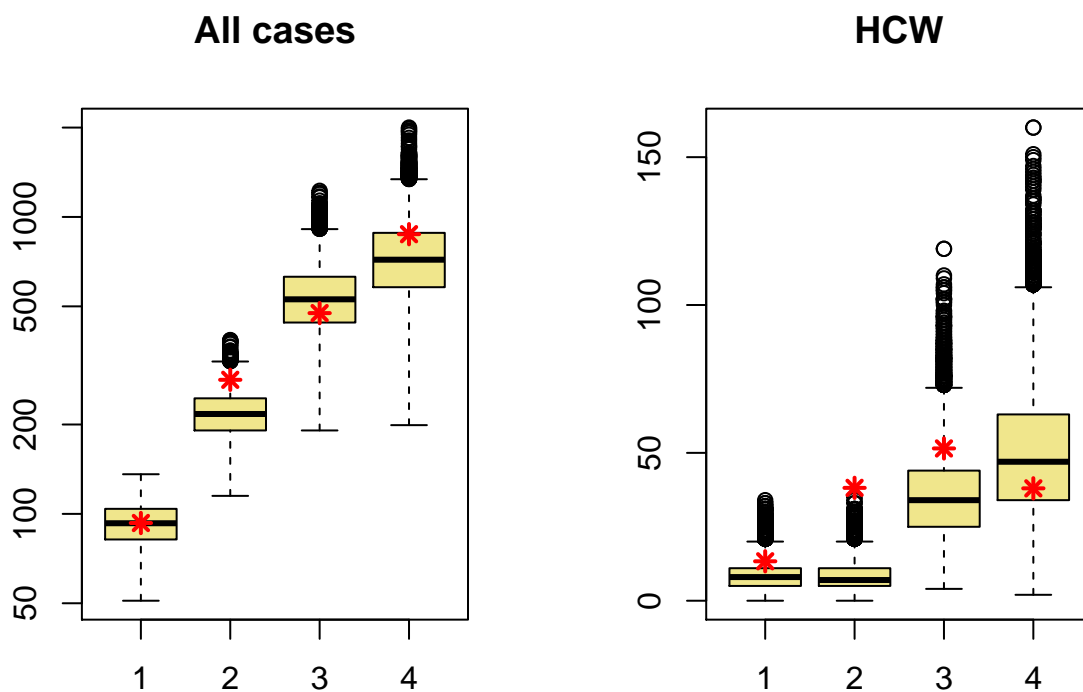


Figure 4: Comparison between the total number of reported cases (red asterisks) and model-generated distribution (box-and-whisker plots) during four generations of the epidemic, starting 4 July 2014. Shown are values for all cases (left panel) and cases among health care workers (right panel).

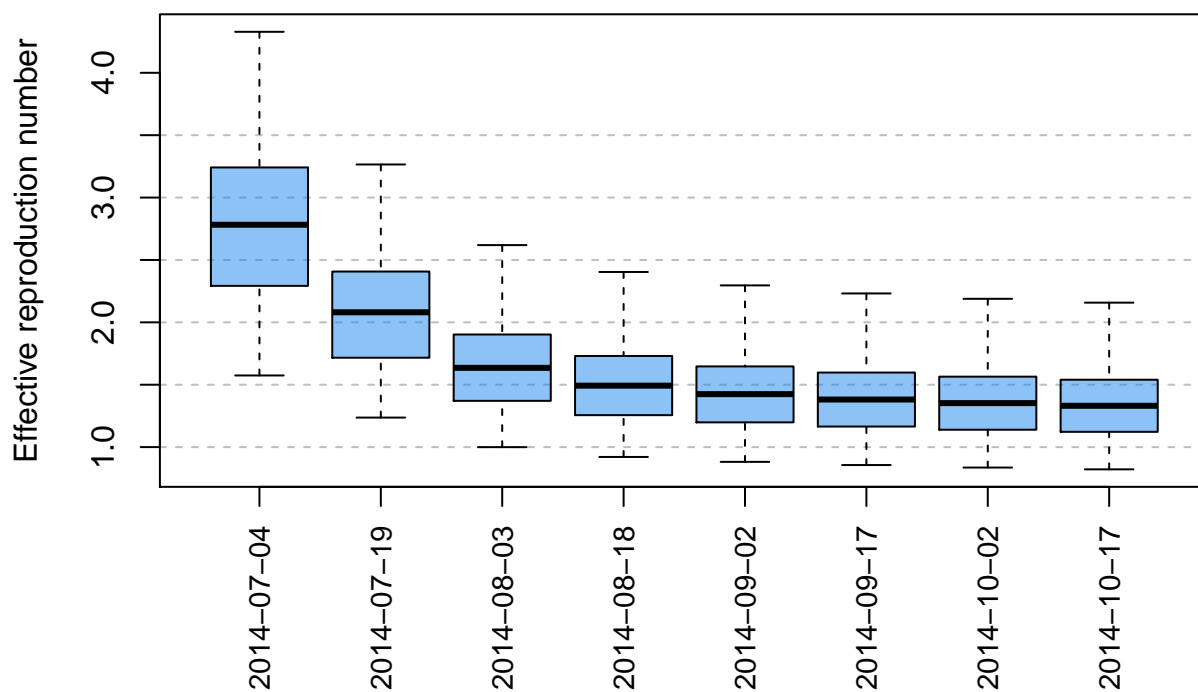


Figure 5: Effective reproduction numbers for Ebola virus in Liberia from July-October 2014.

## Forecasts and containment

Simulated trajectories illustrating the possible outcomes starting on 2 September assuming baseline conditions are shown in Figure 6. The median projected total epidemic size by 31 December is 130,862 cases (inter-quartile range: 44,560 to 396,706). The top panel shows the range of trajectories for 10,450 simulations distributed over 1,045 plausible parameter sets. An interpolation to project the daily number of persons seeking hospitalization is contained in the online supplementary materials. Projected epidemic size by 31 December for all five scenarios is shown in Figure 7.

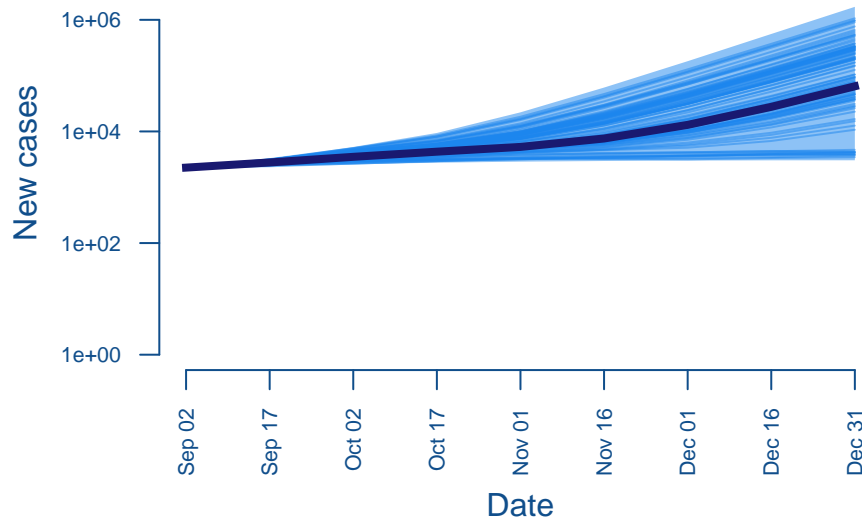


Figure 6: Number of cases in each infection generation when transmission occurs at the baseline rate. Dark blue lines show 100 stochastic realizations of the model. Shaded region shows 95% quantiles over 10,450 realizations; x-axis is the final date of the infection generation, e.g., 17 September is for all cases in the infection generation beginning 2 September.

Scenario A assumes that the Department of Defense (DoD) improvements to hospital capacity constitute the main intervention against the continued spread of Ebola virus in West Africa. In this scenario, an additional 1,700 hospital beds become available between 25 October and 28 December at a rate of one 100-bed facility every four days. This interpolation is based on media reports that the first DoD unit is expected to come online on 25 October and that all units are to be complete by the end of 2014. Results suggest that an initial downturn in cases is to be expected based on isolation, but that capacity will be outstripped by the continuing rise in cases. These results are consistent with observations since 2 September (see online supplement). While these results do predict a temporary downturn, they do not imply that hospitalization is exclusively responsible for this trend. Particularly, public compliance with burial policies, actions taken to increase personal safety, and deterioration in reporting may all also play a role. The median total projected epidemic size by 31 December is 51,202 cases (inter-quartile range: 37,868 to 152,453).

Scenario B assumes that the main line of intervention will be further improvements to hospital capacity in excess of DoD improvements in Scenario A. In this scenario, an additional 6,800 “bed equivalents” (which may include Ebola Community Care units as well as other units) become available between 25 October and 28 December (including the 1,700 ETU beds from Scenario A). The outcome of this scenario is interesting because it shows that improved treatment facilities are not enough to ensure containment (see online supplement). As above, the increased availability of treatment slows transmission for a time, but the outbreak outgrows capacity and takes off again. The median total projected epidemic size by 31 December is 51,260 cases (inter-quartile range: 37,868 to 81,237). Thus, although the upper end of the distribution is reduced, the median and lower end are similar to Scenario A, suggesting that hospital capacity is unlikely to be the limiting factor after the DoD improvements are complete.

Scenario C assumes that improved hospital capacity is complemented by improved public compliance with

## Projected epidemic size by end of 2014

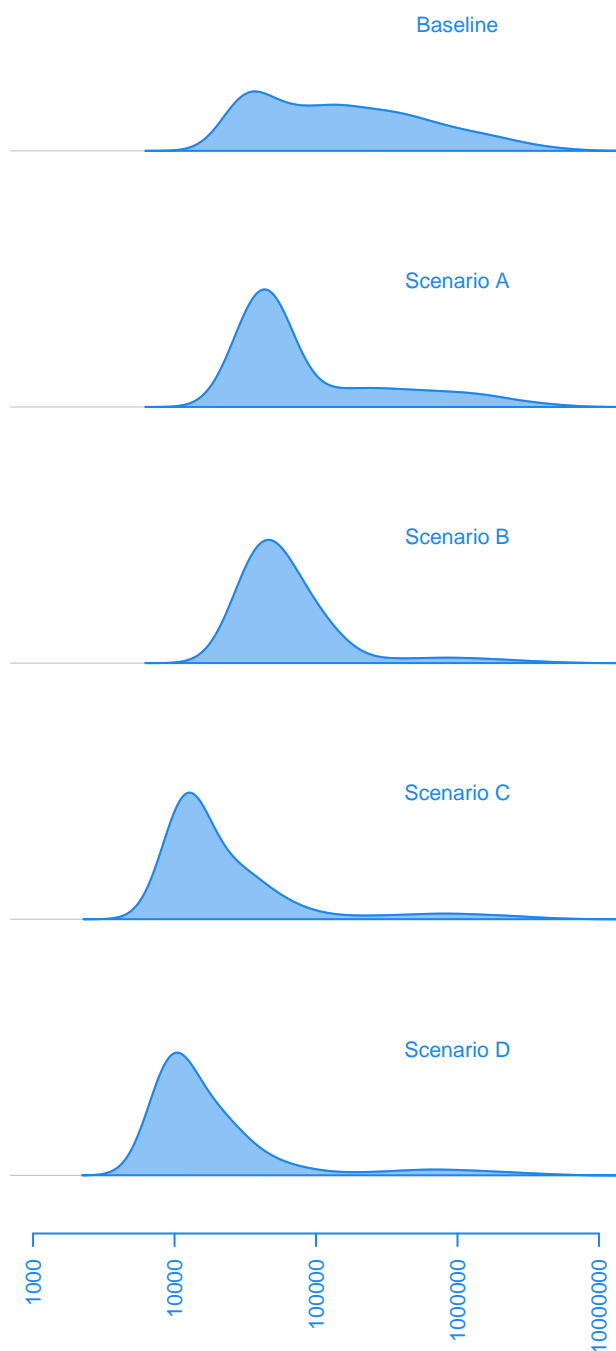


Figure 7: Distribution of number of cases by December 31, 2014 in five scenarios. Scenario A reflects increased hospital capacity from US DoD commitment of 15 September. Scenario B assumed significantly increased hospital capacity in excess of Scenario A. Scenario C reflects significantly increased hospital capacity and increased hospitalization rates. Scenario D reflects significantly increased hospital capacity and significantly increased hospitalization.

recommendations. In this scenario, the fraction of infected persons seeking hospitalization is increased from its baseline (a variable number around 60%) to 85% in addition to the increased hospital capacity envisioned in Scenario B. The expected (median) outcome of this scenario is containment, although some parameterizations cannot be contained by this strategy (see online supplement). The median total projected epidemic size by 31 December is 14,829 cases (inter-quartile range: 11,608 to 30,192).

Although the expected (median) solution to Scenario C is rapid containment with new cases peaking in mid-December, this is not guaranteed. There are several plausible parameterizations for which the interventions are inadequate. We therefore investigated a further scenario (Scenario D) designed to achieve containment. In this scenario, the number of additional bed equivalents is again 6,800 and public compliance with hospitalization is 99%. A majority of parameterizations result in containment (see online supplement).

Since containment is achieved by a majority of parameterizations of this scenario, we ran the simulation until elimination in a majority of cases. The size and duration of 78% of simulated epidemics ending by mid-summer are summarized in the online supplement. Panels on the left show the cumulative probability distribution for outbreak size (top) and duration (bottom). The yellow band shows the inter-quartile range while the median is indicated by a dashed line. Panels on the right show histograms of outbreak size and duration from the 10,450 simulations. These results show that if the epidemic progresses as envisioned by Scenario D, the total epidemic size is expected to be  $\approx 12,285$  (inter-quartile range: 9,205 to 22,984) with elimination by mid-March.

## Discussion

The transmission of Ebola virus in West Africa continues to give rise to high mortality and morbidity. Part of the challenge in predicting the progression of the epidemic lies in the fundamentally different ways in which transmission occurs: infection of hospital workers, community care givers and those preparing bodies for funerals (World Health Organization 2014d). Additionally, the timeframe and effectiveness of increased hospital capacity compounds the problem of prediction (Torjesen 2014), whether it is aimed at anticipating demand for hospitalization or determining the level and speed of intervention needed to bring the outbreak under control. Our approach was to represent heterogeneity in transmission and time-varying intervention in a multi-type branching process model (Jagers and Athreya 1997) that offers analytic tractability, efficient simulation and the flexibility to investigate a wide range of intervention scenarios. It is closely related to sources of data; for example, stratifying cases into hospital-treated versus community-treated allows for estimating under-reporting which is thought to be large for the current epidemic (Gomes et al. 2014).

Analytical insight, particularly the derivation of a reproductive ratio, is useful when parameter estimates (such as the hospitalization rate) are uncertain, since the sign and magnitude of their effects on transmission can be derived. Besides recovering a full expression for the basic reproductive ratio, simplifying assumptions such as assuming that funeral-associated transmission can be reduced to zero, yield further understanding. In particular, our model shows how the additional exposure to health care workers in a hospital environment ( $\beta$ ) combines with both the reduced transmission in that environment ( $\alpha$ ) and the hospitalization rate ( $h$ ) to determine when community (versus hospital) transmission will dominate (*i.e.* when  $1 - h > \alpha\beta$ ). Such formulas may provide “rules of thumb” to help guide infection control or could improve practical decision making by regularly updating estimates of core parameters through surveillance within health facilities.

The approach we have taken to model parameterization is novel. A more familiar approach is to propose a deterministic or stochastic model that is then fit by minimizing an objective function on the errors, *e.g.*, sum of squares or negative log likelihood of the data given the model (Legrand et al. 2007). Statistical interpretation of such models (such as hypothesis tests or confidence intervals) relies heavily on the parametric specification of both the process model and the observation model. If the proposed models are not good approximations to their respective contributions to the data-generating process, then these quantities may be quite biased. Moreover, such models are ineffective when they are overparameterized. Our approach—the construction of plausible parameter sets that are both epidemiologically sensible and can reproduce observed properties of the epidemic—seeks to better understand the space of models consistent with the data. The cost of this approach is that the results do not admit probabilistic interpretations, hypothesis tests, or

the construction of confidence intervals. A byproduct is that the identifiability of parameters (which is compromised by overparameterization) is no longer an obstacle to model construction and forecasting. If two parameters, say  $a$  and  $b$ , are highly correlated (not simultaneously identifiable) so that either the model with large  $a$  and small  $b$  or large  $b$  and small  $a$  are both consistent with the data, then the plausible set will include parameter combinations with examples of both kinds (but not large  $a$  and large  $b$  or small  $a$  and small  $b$ , say). It may be that these differences are in fact irrelevant to the eventual behavior of the model, in which case the space of possible solutions will be small. Alternatively, it may be that these are just the parameters that most substantially influence alternative outcomes, in which case the space of possible solutions will be large. By seeking bounds on the range of outcomes rather than a unique causal story, the method of plausible parameter sets avoids technical problems with model identifiability and more accurately emphasizes the kind of uncertainty prevalent under emergent conditions while focusing attention on the property of most practical interest: the possible future trajectories of the epidemic. In conclusion, we believe that the method of plausible parameter sets is a good starting point for exploring entire families of models and for setting bounds on the range of possible outcomes. It is a first step toward the construction of models for probabilistic inference.

In this study, we have focused on Liberia, one of the worst-hit countries during the current outbreak. The ramping up of hospital capacity in Liberia was dramatic during late August 2014, adding approximately 300 beds. Throughout September, that sustained effort led to an additional ~300 beds. This heterogeneous increase in capacity over time was incorporated into our model. We investigated alternative hospital capacities and demands in a set of plausible alternative scenarios. The best and worse outcomes of these scenarios vary dramatically in the forecasted epidemic size. Median estimates are at around 130,000 cases by 31 December 2014 assuming a baseline scenario without increased hospital capacity. This is reduced to around 50,000 when capacity is ramped up to ~1,700. Further increases in hospital capacity reduce the upper bounds, but not the median. If the hospitalization rate can be increased to 85%, median predictions are of containment, with an effective reproductive ratio  $<1$ . In conclusion, this exercise suggests that in the absence of rapid hospitalization of most cases, none of the proposed scenarios for increasing hospital capacity is likely to achieve containment.

Branching process models use offspring distributions to simulate forward in time. Here, the offspring of an infectious individual refers to the new cases generated from that infectious individual. This is the type of data that is frequently reported, even during early stages of an outbreak. Models that require contact-tracing data are complicated by the fact that there is uncertainty about whether contact is effective or not. For example, how many “contacts” of an infectious individual that gets on a plane are sufficiently intimate that infection is even a causal possibility? Ambiguities about the causal relevance of contacts of different kinds complicate models expressed in terms of attack rates. By focusing on the empirical offspring distributions in various transmission settings, one is able to build, simulate and analyze a model with the key epidemiological features, and to investigate a wide range of mitigation scenarios. In our case, the result was a multi-type branching process that separated the location that infection was acquired from the sites generating new infections. This approach captures the behavioral aspects of transmission that are often lacking in models (Funk, Salathé, and Jansen 2010). Awareness of Ebola in the community and public education mean that community-acquired transmission is increasingly likely to lead to demand for hospitalization. While our methods are focused on the current Ebola outbreak in West Africa, they apply to a broad class of infectious diseases.

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# Ebola cases and health system demand in Liberia: Supplementary Materials

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## Introduction

This document contains supplementary material for the paper “Ebola cases and health system demand in Liberia” by the UGA-MIDAS Ebola Modeling Group.

## Effective reproduction number ( $R_{eff}$ )

From the independence of the mixture components, we obtain the *mean matrix* for transmission generations defined in terms of treatment location.

$$M = \begin{bmatrix} Nq\alpha\beta\theta + h\lambda_h & (1-h)\lambda_h \\ h(\theta Nqg + (1-g)(Nq\theta + \phi)) & (1-h)(\theta Nqg + (1-g)(Nq\theta + \phi)) \end{bmatrix} \quad (1)$$

The two eigenvalues of this matrix are:

$$\Lambda_1 = \frac{1}{2}(Nq(1-h+\alpha\beta)\theta + (g-1)(h-1)\phi + h\lambda_h + \sqrt{((Nq\phi(h+\alpha\beta-1) - (g-1)(h-1)\phi)^2 + h\lambda_h(2Nq\phi(1-h+\alpha\beta) + 2\phi(g-1)(h-1) + h\lambda_h))}) \quad (2)$$

$$\Lambda_2 = \frac{1}{2}(Nq(1-h+\alpha\beta)\theta + (g-1)(h-1)\phi + h\lambda_h - \sqrt{((Nq\phi(h+\alpha\beta-1) - (g-1)(h-1)\phi)^2 + h\lambda_h(2Nq\phi(1-h+\alpha\beta) + 2\phi(g-1)(h-1) + h\lambda_h))}) \quad (3)$$

The dominant eigenvalue ( $\Lambda$ ) is the long run growth rate of the epidemic and provides a threshold criterion such that outbreak will grow if  $\Lambda > 1$  and decline if  $\Lambda < 1$ . In this model, which ignores susceptible depletion,  $\Lambda$  is always the effective reproduction number ( $R_{eff}$ ) in that it is the average number of secondary infections in a population comprised of community-treated and hospital-treated cases at its stable distribution. If evaluated at  $t = 0$ ,  $\Lambda$  may also be interpreted as the basic reproductive ratio ( $R_0$ ). A special case of interest is the complete elimination of cases in the community generated by cases treated in the hospital ( $\lambda_h = 0$ ). In this case, the eigenvalues are  $\Lambda_1 = \alpha\beta\theta Nq$  and  $\Lambda_2 = (1-h)((1-g)(\theta Nq + \phi) + g\theta Nq)$ . Which  $\Lambda$  will be dominant depends on the values of  $\alpha$ ,  $\beta$ ,  $h$ ,  $g$ , and  $\phi$ , so that eventually either community transmission or hospital transmission drives the persistence of the infection. Further insight may be obtained by inspecting the case where funeral transmission is reduced to zero ( $\phi = 0$ ). Then,  $\Lambda_2 = (1-h)\theta Nq$ . Community transmission dominates in this case if  $1-h > \alpha\beta$ . Note that where hospital transmission dominates ( $\Lambda_1 > \Lambda_2$ ) the elasticities of the parameters are identical. This means that proportional changes in each quantity have identical effect (halving the contact number is equivalent to halving the effectiveness of infection control is equivalent to halving the increased contact rate in health care facilities, *etc.*).

## Supplementary Figures

Figure 1 shows the distribution of five case classifications over the time period used for fitting. These are: (1) number of health care workers infected (HCW), (2) total number of reported cases, (3) total cases, (4) fraction of cases that were hospital-acquired, and (5) fraction of cases associated with funeral preparation and burial. For (1) and (2), the red line corresponds to the WHO reported number during the interval. For (3), the red line corresponds to total cases obtained by multiplying the number of reported cases by 2.5, the presumed factor of under-reporting. Importantly, the number of funeral acquired cases is consistent with anecdotes reported by Rivers et al (2014). The fraction of cases that are hospital-acquired is somewhat lower than anecdotally reported. Figure 2 projects daily hospital demand (new patients seeking hospitalization) according to the baseline scenario. Figures 3 and 4 illustrate the range of trajectories and daily hospital demand associated with Scenario A. Figures 5 and 6 illustrate the range of trajectories and daily hospital demand associated with Scenario B. Figures 7 and 8 illustrate the range of trajectories and daily hospital demand associated with Scenario C. Figures 9 and 10 illustrate the range of trajectories and daily hospital demand associated with Scenario D. Figure 11 shows the total epidemic duration and outbreak size for the 78% of simulations of Scenario D terminating in mid summer 2015.

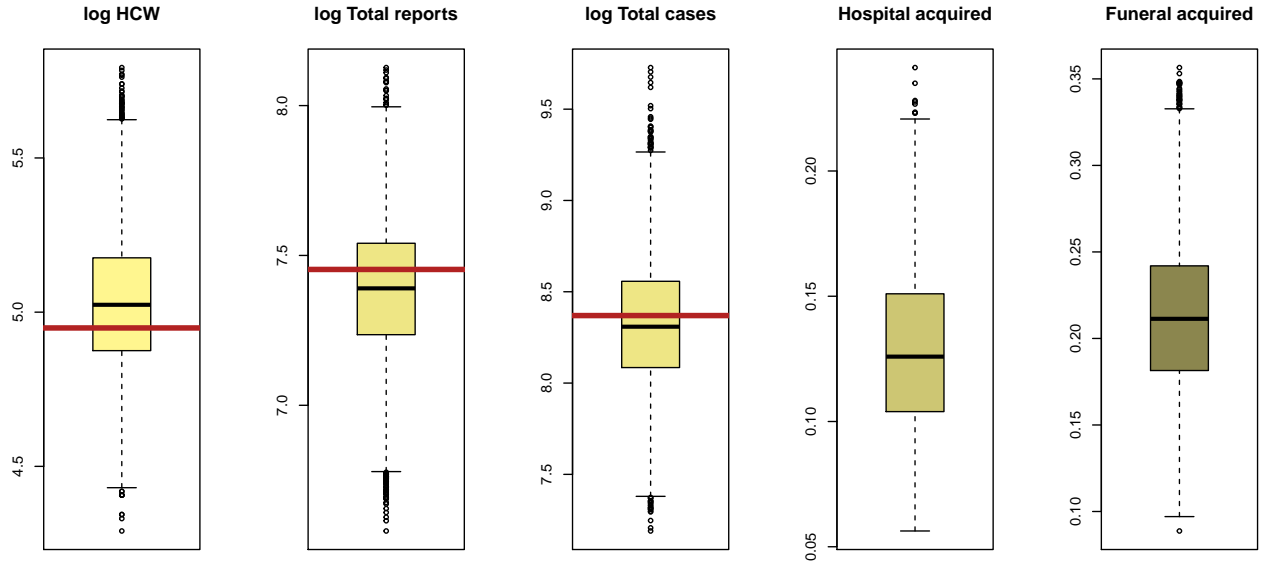


Figure 1: Cumulative reported cases in data (red lines) and model simulations (box-and-whisker plots). The left three panels show results for health care workers, reported cases, and reported and unreported cases (assuming 2.5 fold under-reporting). The remaining panels show the model-predicted distributions of hospital-acquired infections and funeral-acquired infections.

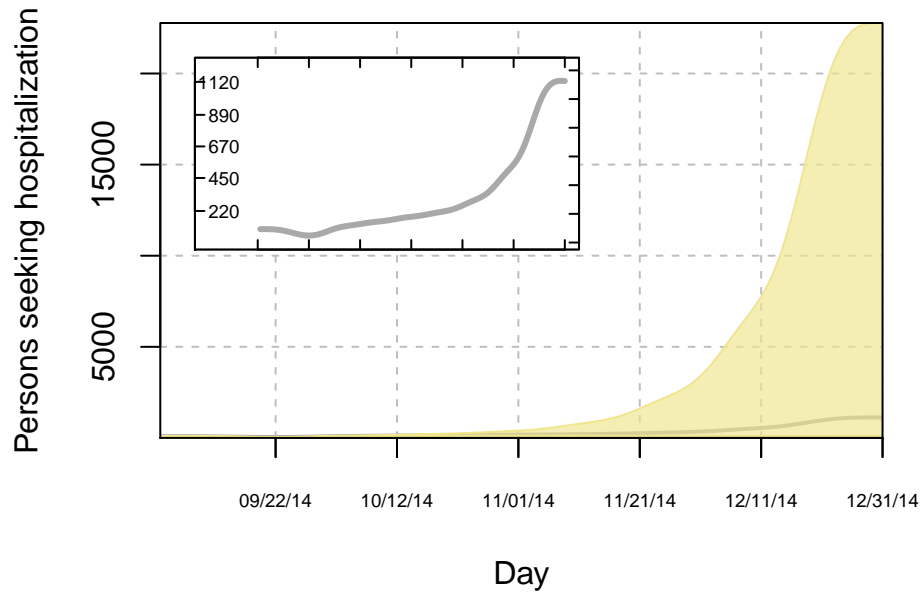


Figure 2: Daily number seeking hospitalization (bottom) when transmission occurs at the baseline rate. Inset plot shows the median daily number of cases.

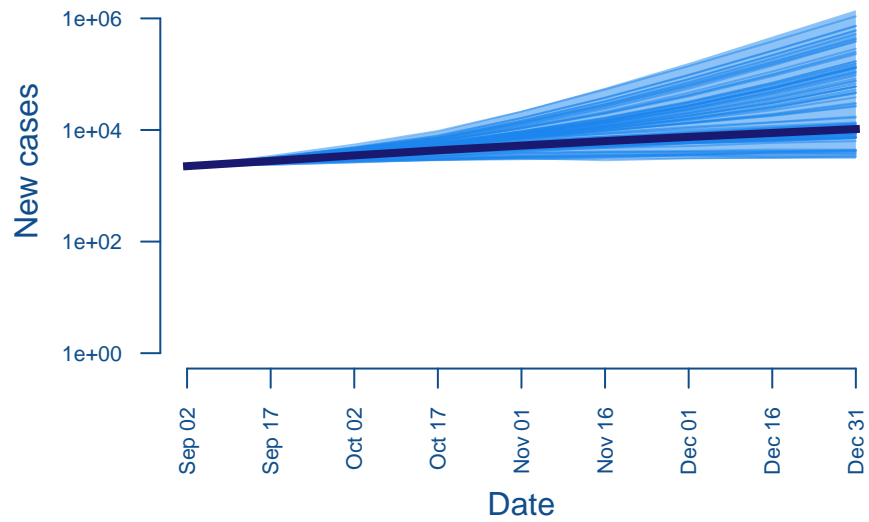


Figure 3: Number of cases in each infection generation under Scenario A.

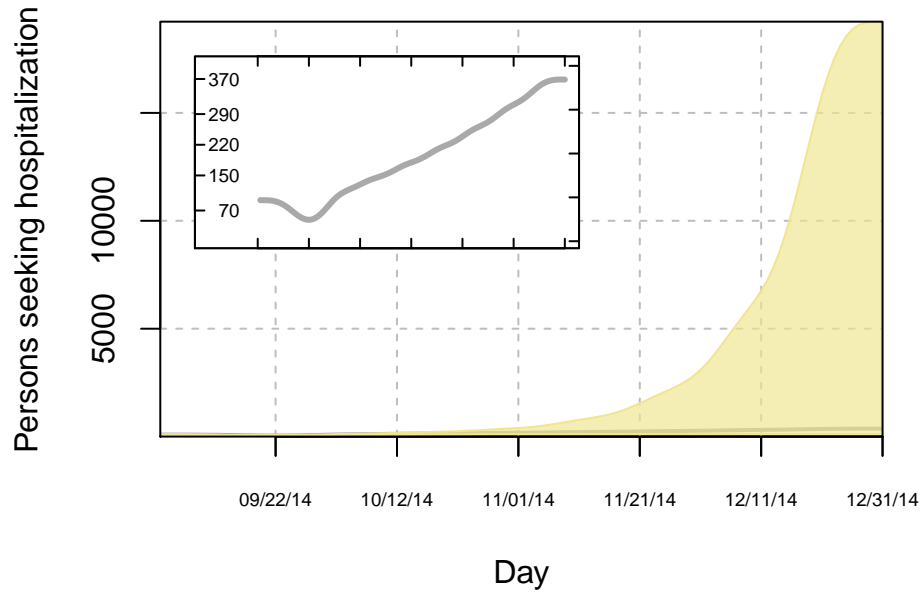


Figure 4: Daily number seeking hospitalization (bottom) according to Scenario A. Inset plot shows the median daily number of cases.

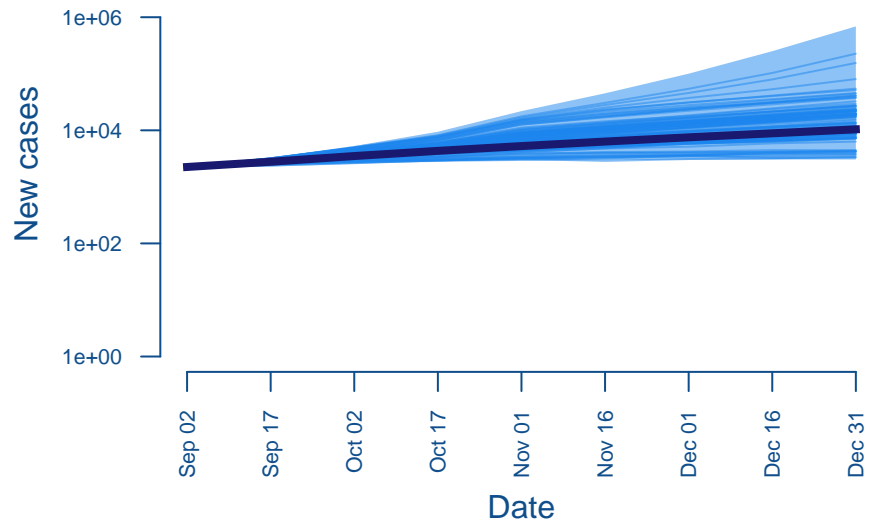


Figure 5: Number of cases in each infection generation under Scenario B.

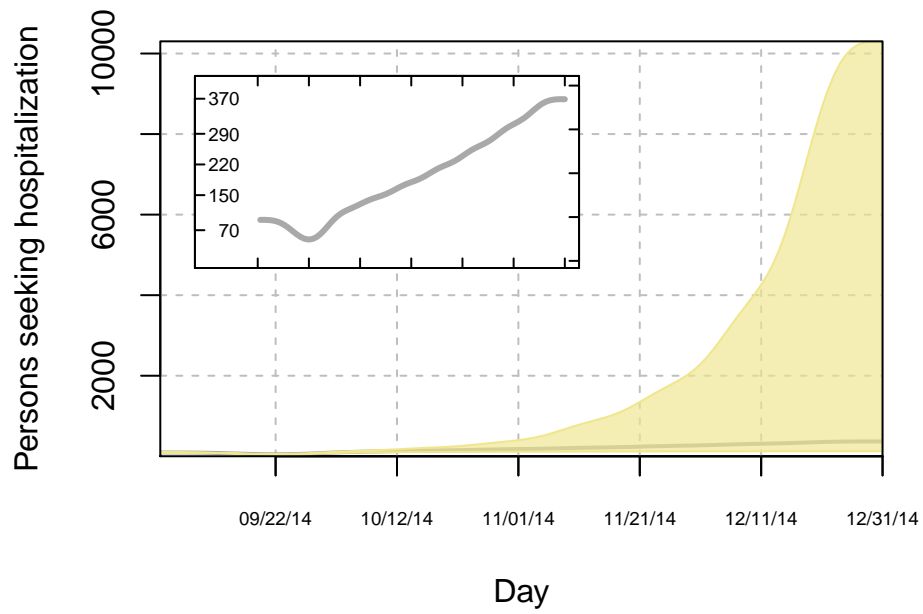


Figure 6: Daily number seeking hospitalization (bottom) according to Scenario B. Inset plot shows the median daily number of cases.

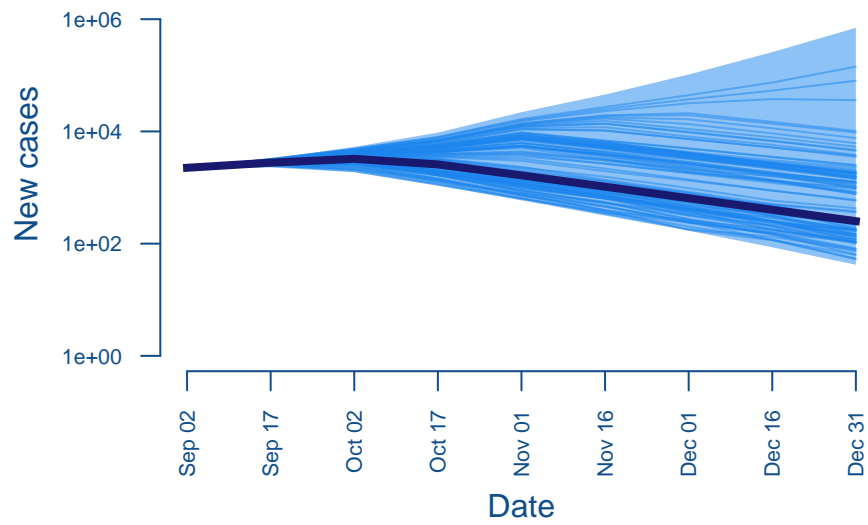


Figure 7: Number of cases in each infection generation under Scenario C.

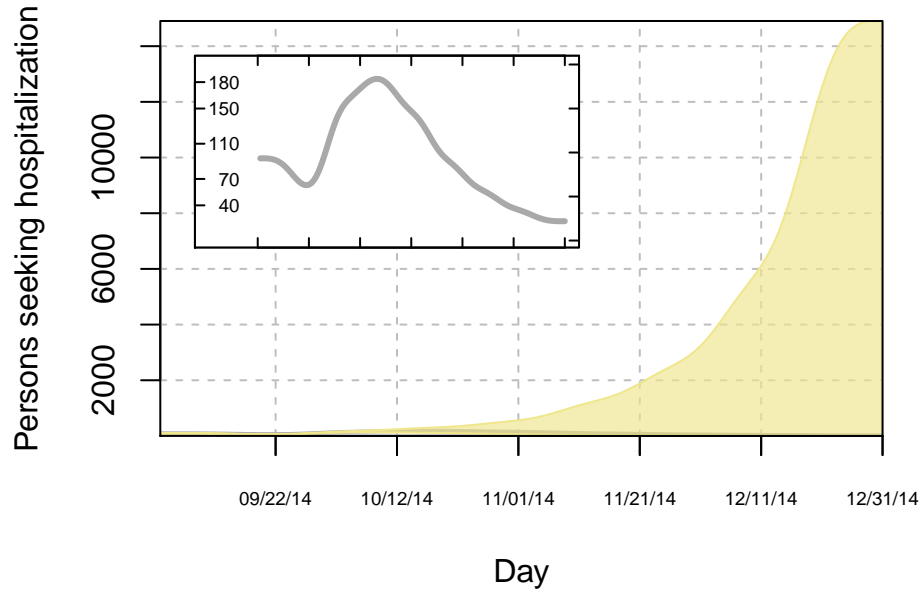


Figure 8: Daily number seeking hospitalization (bottom) according to under Scenario C. Inset plot shows the median daily number of cases.

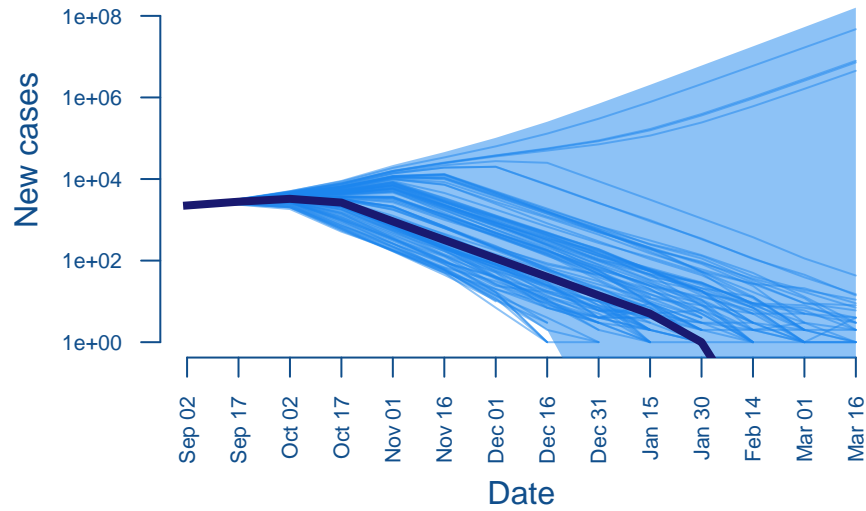


Figure 9: Number of cases in each infection generation under Scenario D.

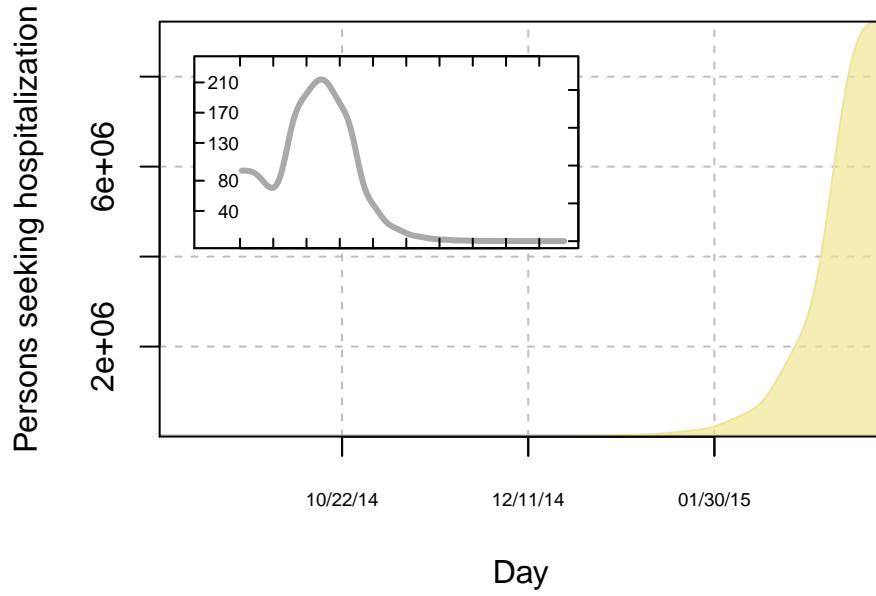


Figure 10: Daily number seeking hospitalization (bottom) according to under Scenario D. Inset plot shows the median daily number of cases.

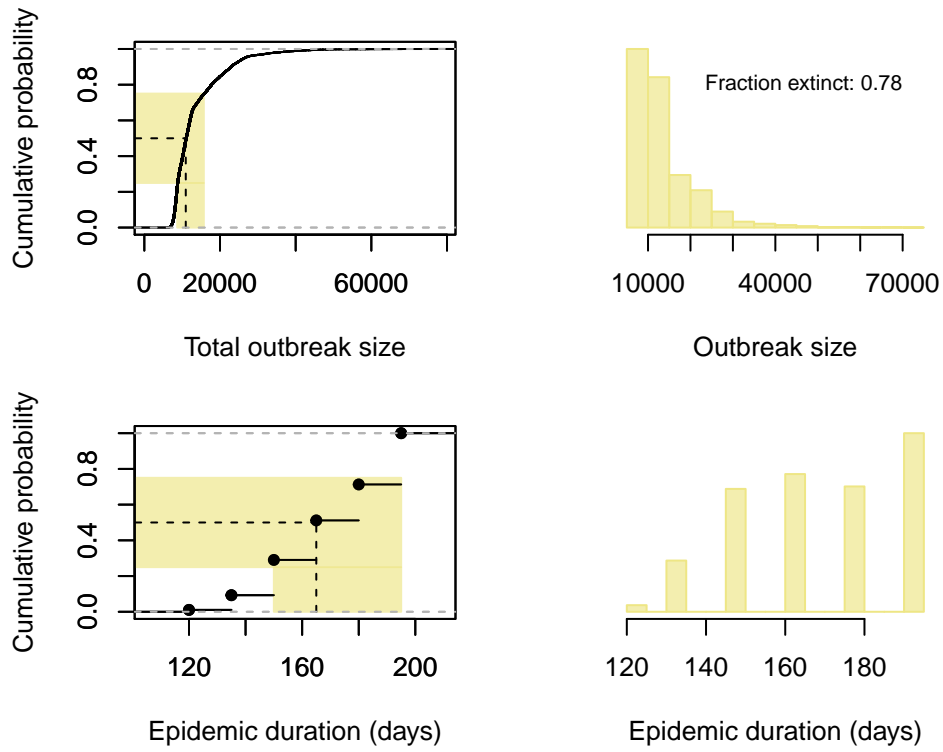


Figure 11: Cumulative distribution function (left) and histogram (right) of the total epidemic size (top) and epidemic duration in days after 2 September 2014 (bottom) in a containment scenario (Scenario C).